REMARKS

Claims 1-11 and 15-17 are pending in the application. Claims 15-17 to the non-elected invention may be later rejoined or may be the subject matter of one or more divisional applications.

Applicants elect with traverse Group I, Claims 1-11, drawn to a pharmaceutical formulation. The claims encompassing the elected invention are claims 1-11.

Applicants traverse the restriction requirement and election of species/invention as follows:

The Examiner asserts that "Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1, because, under PCT Rule 13.2, they lack the same or corresponding special technical features". The Examiner asserts that "the inventions lack the same or corresponding special technical features for the following reasons: the special technical feature in the instant claims a composition comprising of levothyroxine, 60-85% of microcrystalline cellulose with a particle size of less than 125 μm, and 5-30% of pregelatinised starch". The Examiner cites MITRA (US 5,955,105) and RUSZKAY (US 5,975,600) in evidence.

It is Applicants' position that the special technical feature of the instant claims is a pharmaceutical formulation comprising:

a) an effective amount of levothyroxine sodium;

b) microcrystalline cellulose having a mean particle size of less than 125um, present in 60 to 85% w/w amount; and

c) pregelatinised starch present in 5 to 30% w/w amount.

Applicants would point out that MITRA , however, is directed to stabilized pharmaceutical preparations containing levothyroxine sodium (column 1, lines 12-14), achieved by using:

-a water soluble glucose polymer (see claim 1), such as maltodextrins (see column 4, lines 15-16); and

-a partially soluble or insoluble cellulose polymer (see claim 1).

It should be noted that the use of a water soluble glucose polymer in the formulation is an essential feature of the invention in MITRA and of the entire disclosure of MITRA (see claim 1).

Example 10 of MITRA (as identified by the Examiner) employs the specific components:

-microcrystalline cellulose as the partially soluble or insoluble cellulose polymer, and

-starch as the water soluble glucose polymer, that is, the starch used in Example 10 must be water soluble starch (since this is an essential feature of the invention in MITRA).

The Examiner has asserted that Example 10 of MITRA uses pregelatinised starch. Applicants respectfully refute this assertion. There is no such disclosure in Example 10 of MITRA. The starch used in MITRA is water soluble. It should be noted that pregelatinised starch is not water soluble. The European Pharmacopoeia (2002), cited in the present application (page 2, lines 36-37 and also enclosed herewith), states on page 1438 that pregelatinised starch swells in cold water (which clearly means that it does not dissolve in water).

The differences between the special technical feature of the instant claims and Example 10 of MITRA are therefore:

(I) in the present application, the microcrystalline cellulose has a particle size of less than 125um, and

(II) instead of a water soluble glucose polymer, (i.e. the water soluble starch of Example 10 of MITRA), the instant claims employ pregelatinised starch.

In respect of the special technical feature of the instant claims, one of the unexpected technical effects observed when both

a) 60 to 85% w/w microcrystalline cellulose having a particle size of less than 125um and

b) 5 to 30% w/w pregelatinised starch

are used together in the formulation, is that the active substance, levothyroxine sodium, is more stable and fewer impurities are observed than in the marketed

formulation of Eltroxin, as indicated on page 7 of the instant application, conclusions (A) and (B) of the present application (PCT Application WO 2005/004849 A2 as published in English). This effect on stability by use of the present components could not have been predicted by a skilled person from a reading of MITRA.

The Examiner cites RUSZKAY as a disclosure of microcrystalline cellulose in a particle size of 5-50um (col 3, line 38). The Examiner will appreciate that RUSZKAY is in an entirely different field from that of MITRA.

RUSZKAY is directed to making a bulking agent in oil-based foods or food components (col. 2, lines 31-36 of RUSZKAY), whereas MITRA is directed to stabilized pharmaceutical preparations containing levothyroxine sodium (column 1, lines 12-14).

There is no motivation for a person skilled in the art of stabilizing pharmaceuticals to take the teaching of MITRA and combine it with the teaching of RUSZKAY, because RUSZKAY is in the field of bulking agents for foodstuffs, and has nothing to do with stabilization, even less to do with pharmaceuticals. Even if he *were* to combine the teachings, he would still be missing the second difference between MITRA and the instant invention (labelled (II) above), namely, that instead of a water soluble glucose polymer, (i.e. the water soluble starch of Example 10 of MITRA), the instant invention employs pregelatinised starch.

There is no mention, nor even a suggestion, anywhere in MITRA to replace the water soluble starch of Example 10 with pregelatinised starch. As mentioned above, pregelatinised starch is not water soluble; the disclosure of MITRA focuses entirely on the use of a water soluble glucose polymer (as an essential feature), together with a partially soluble or insoluble cellulose polymer to achieve a stable formulation of thyroxine. MITRA does not contemplate the use of insoluble glucose polymers in the formulations to achieve stability. A skilled person would not be motivated to go against the express teaching of MITRA and use an insoluble glucose polymer to achieve a stable formulation with any reasonable expectation of success. RUSZKAY is also of no help in this regard as it does not mention or suggest pregelatinised starch.

In summary, the disclosure of MITRA, when considered either alone or in combination with RUSZKAY, provides no motivation for the skilled person to make changes to the formulation of MITRA such that he would arrive at the stable formulation as per the special technical feature of the instant claims, let alone allow him to predict that the present formulation would be a stable one. The stable nature of the formulation of the instant claims is completely unexpected and cannot be predicted by the skilled person from a reading of the prior art documents MITRA or RUSZKAY. The stable formulation of levothyroxine sodium as per the special technical feature of the instant claims therefore defines a clear contribution over the disclosures of MITRA and RUSZKAY.

Accordingly, it is respectfully requested that all restriction/election of the claims be reconsidered and withdrawn and that the application as amended be allowed.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

Bonnie L. Deppenbrock
Attorney for Applicant
Registration No. 28,209

Date: 27 June 2008

GlaxoSmithKline
Corporate Intellectual Property
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
Phone: 919-483-1577
Facsimile: 919-483-7988

Identification
Dissolve 20 mg in the minimum volume of *chloroform* and evaporate to dryness in a current of nitrogen at room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of stanozolol *(RS 322)*.

Specific optical rotation In a 1% w/v solution in *chloroform*, +34° to +40°, calculated with reference to the dried substance, Appendix V F.

Related substances Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel H* as the coating substance and a mixture of 90 volumes of *chloroform* and 10 volumes of *methanol* as the mobile phase. Apply separately to the plate 5 µl of each of two solutions of the substance being examined in a mixture of 1 volume of *methanol* and 4 volumes of *chloroform* containing (1) 2.0% w/v and (2) 0.010% w/v. After removal of the plate, allow it to dry in air, spray with *ethanolic sulphuric acid (20%)*, heat at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 100° at a pressure not exceeding 0.7 kPa, loses not more than 1.0% of its weight. Use 1 g.

Assay Dissolve 0.7 g in 50 ml of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each ml of 0.1M *perchloric acid VS* is equivalent to 32.85 mg of $C_{21}H_{32}N_2O$.

Storage Stanozolol should be kept in a well-closed container and protected from light.

Action and use Anabolic steroid.

Preparation
Stanozolol Tablets

Pregelatinised Starch

Pregelatinised Starch complies with the requirements of the 3rd edition of the European Pharmacopoeia [1267]. These requirements are reproduced after the heading 'Definition' below.

When Pregelatinised Starch is prepared from *Zea mays*, the title Pregelatinised Maize Starch may be used.

Ph Eur

DEFINITION

Pregelatinised starch is starch, apart from wheat starch, that has been mechanically processed in the presence of water, with or without heat to rupture all or part of the starch granules and subsequently dried. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics.

CHARACTERS

A white or yellowish-white powder, swelling in cold water.

IDENTIFICATION

A. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R* it presents irregular, translucent, white or yellowish-white flakes or pi... an uneven surface. Under polarised light, (betw... crossed nicol prisms), starch granules with a dia... cross intersecting at the hilum may be seen.

B. Disperse 0.5 g in 2 ml of *water R* without heati... add 0.05 ml of *iodine solution R1*. A reddish-violet ... colour is produced.

TESTS

pH *(2.2.3)*. Shake 5.0 g with 25.0 ml of *carbon dioxi... water R* for 60 s. Allow to stand for 15 min. The pH ... solution is 4.5 to 7.0.

Iron *(2.4.9)*. Shake 0.75 g with 15 ml of *dilute hydro... acid R*. Filter. The filtrate complies with the limit test ... iron (20 ppm).

Oxidising substances *(2.5.30)*. It complies with the ... for oxidising substances.

Sulphur dioxide *(2.5.29)*. Not more than 50 ppm.

Foreign matter *(2.8.2)*. Examined under a microscope ... using a mixture of equal volumes of *glycerol R* and *water ...* not more than traces of cell walls and of cytoplasmic ... residues are present.

Loss on drying *(2.2.32)*. Not more than 15.0 per cent, ... determined on 1.000 g by drying in an oven at 130°C for ... 90 min.

Sulphated ash *(2.4.14)*. Not more than 0.6 per cent, ... determined on 1.0 g.

Microbial contamination Not more than 10^3 bacteria ... and not more than 10^2 fungi per gram, determined by ... plate-count *(2.6.12)*. It complies with the test for ... *Escherichia coli (2.6.13)*.

STORAGE

Store in a well-closed container.

LABELLING

The herbal origin of Starch, pregelatinised is stated.

Stearic Acid

Stearic Acid complies with the requirements of the 3rd edition of the European Pharmacopoeia [1474]. These requirements are reproduced after the heading 'Definition' below.

Action and use Pharmaceutical aid.

Ph Eur

DEFINITION

Stearic acid is obtained from fats or oils from a vegetable or animal source and is a mixture consisting mainly of stearic acid ($C_{18}H_{36}O_2$; M_r 284.5) and palmitic acid ($C_{16}H_{32}O_2$; M_r 256.4). It contains different nominal amounts of $C_{18}H_{36}O_2$; stearic acid 50 contains 40.0 per cent to 60.0 per cent, stearic acid 70 contains 60.0 per cent to 80.0 per cent and stearic acid 95 contains at least 90.0 per cent of $C_{18}H_{36}O_2$. The sum of the contents of $C_{18}H_{36}O_2$ and $C_{16}H_{32}O_2$ is not less than 90.0 per cent for stearic acid 50 and stearic acid 70 and not less than 96.0 per cent for stearic acid 95.

Correspondence between Ph Eur general methods and Appendices of the British Pharmacopoeia is shown on page A8